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Effects of the use of growth hormone in children and adolescents with juvenile idiopathic arthritis: a systematic review

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ABSTRACT

Introduction: Children with juvenile idiopathic arthritis (JIA) often have impaired growth and short stature. There is evidence that the therapeutic use of growth hormone (GH) is useful and safe in these patients.

Objective: To analyze the effects of GH use in patients with JIA.

Method: A systematic review of the literature over the last 18 years in Medline and Embase databases. The criteria were analyzed independently by the researchers. We used the following keywords: "growth hormone", "arthritis, juvenile", "arthritis, rheumatoid", "child" and "adolescent".

Results: Among the 192 identified articles, 20 corresponded to the inclusion criteria. Seventeen longitudinal studies and 3 case reports were found. Most studies analyzed observed increased growth, muscle mass and bone mass using GH. Adverse effects observed were glucose intolerance, diabetes, bone deformities, osteonecrosis, reactivation of the disease and low final height.

Conclusion: The majority of studies reported positive effects after the therapeutic use of GH, but some variability in response to treatment was observed. The combination of growth hormone with other drugs seems to be a good option.

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Efeitos do uso do hormônio de crescimento em crianças e adolescentes com artrite idiopática juvenil: revisão sistemática

R E S U M O

Palavras-chave:

Artrite idiopática juvenil
Hormônio de crescimento
Crianças
Adolescentes

Introdução: Crianças com artrite idiopática juvenil (AIJ) frequentemente apresentam prejuízo no crescimento e baixa estatura. Existem evidências de que o uso terapêutico do hormônio de crescimento (GH) é útil e seguro nesses pacientes.

Objetivo: Analisar os efeitos do uso de GH em pacientes com AIJ.

Método: Fez-se revisão sistemática da literatura nos últimos 18 anos, nas bases de dados Medline e Embase. Os critérios foram analisados pelos pesquisadores de forma independente. Usaram-se os seguintes descritores: *growth hormone*, *arthritis*, *juvenile*, *arthritis*, *rheumatoid*, *child* e *adolescent*.

Resultados: Entre os 192 artigos identificados, 20 corresponderam aos critérios de inclusão. Foram encontrados 17 estudos longitudinais e três relatos de casos. A maioria dos estudos analisados observou um aumento de crescimento, massa muscular e massa óssea com o uso do GH. Os efeitos adversos observados foram intolerância à glicose, diabetes, deformidades ósseas, osteonecrose, reativação da doença e altura final baixa.

Conclusão: A maioria dos estudos relatou efeitos positivos após uso terapêutico do GH, porém certa variabilidade na resposta ao tratamento foi observada. A combinação do hormônio de crescimento com outros medicamentos parece ser uma boa opção.

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Introduction

Juvenile idiopathic arthritis (JIA) is an autoimmune disease and the leading cause of chronic arthritis in pediatric patients. Its annual incidence varies from 2 to 20 cases/100,000 inhabitants, with a prevalence of 15–150 cases/100,000 inhabitants.¹

Its main features are chronic arthritis, and in some cases being associated with multisystem involvement and progression to joint limitations and permanent functional disability.²

The diagnosis of JIA is based on criteria of the International League of Associations for Rheumatology (ILAR) and requires the presence of arthritis in children and adolescents aged under 16 years, that persists for at least six weeks, when excluding the presence of other causes of chronic arthritis.³ According to the literature, the most frequent JIA subtypes are oligoarticular JIA (50–60%), polyarticular JIA (30–35%) and systemic JIA (10–20%).⁴

Children with JIA often exhibit an inadequate growth and short stature, and these effects relate to the extent of organs involved, with the activity and extent of the disease, malnutrition, malabsorption, increased catabolism, associated complications, a constant inflammatory process, and effects of the use of certain medications, being the most relevant of them the glucocorticoids.^{5–8} Several studies have observed improved growth and height rates in patients with JIA treated with growth hormone (GH).^{5,9–25} There are several indications of the use of GH approved for treatment of JIA; however, the use of this hormone can result in adverse events,²⁶ including negative variability in response to treatment which has been observed in some studies of patients with JIA.^{9,10,14,19,20,24,25,27,28}

Due to the high cost and potential side effects,^{9,10,20,27} there are controversies about the ideal indication, the dose, and

duration of the GH therapy in JIA.²⁶ An understanding the indications for therapy with growth hormone and its controversies can facilitate the evaluation of the patient and his/her referral to the best treatment.^{26,29,30} The aim of this study is to analyze the various effects of GH use in patients with JIA, based on the literature review.

Methods

This study consists of a systematic literature review, after a search conducted during the months of July and August 2015, of studies published in the last 18 years (1998–2015). The search of the references was conducted through an electronic database (Medline and Embase) exploration and of the reference list of identified articles by three researchers independently. References that met the inclusion criteria were evaluated, regardless of their journal. The selection of the descriptors used in the review process was conducted in consultation with DeCS (Health Sciences Descriptors by BIREME). In the search, the following descriptors in Portuguese and English were considered: “growth hormone”, “arthritis, juvenile”, “arthritis, rheumatoid”, “child” and “adolescent”.³¹

In the electronic database MedLine, 104 studies were identified, and Embase 88 studies were identified, totaling 192 studies. 64 matching studies were identified, and 128 articles were tabulated on a spreadsheet with data related to the title of the study, journal, year, age group studied, study idiom, evaluated diseases, disease duration, treatment time, therapeutic dose, and possible use of growth hormone as a therapy.

The inclusion criteria were as follows: (1) Original articles; (2) Articles in Portuguese or in English idiom; (3) Articles which used growth hormone as a therapy; (4) Articles that

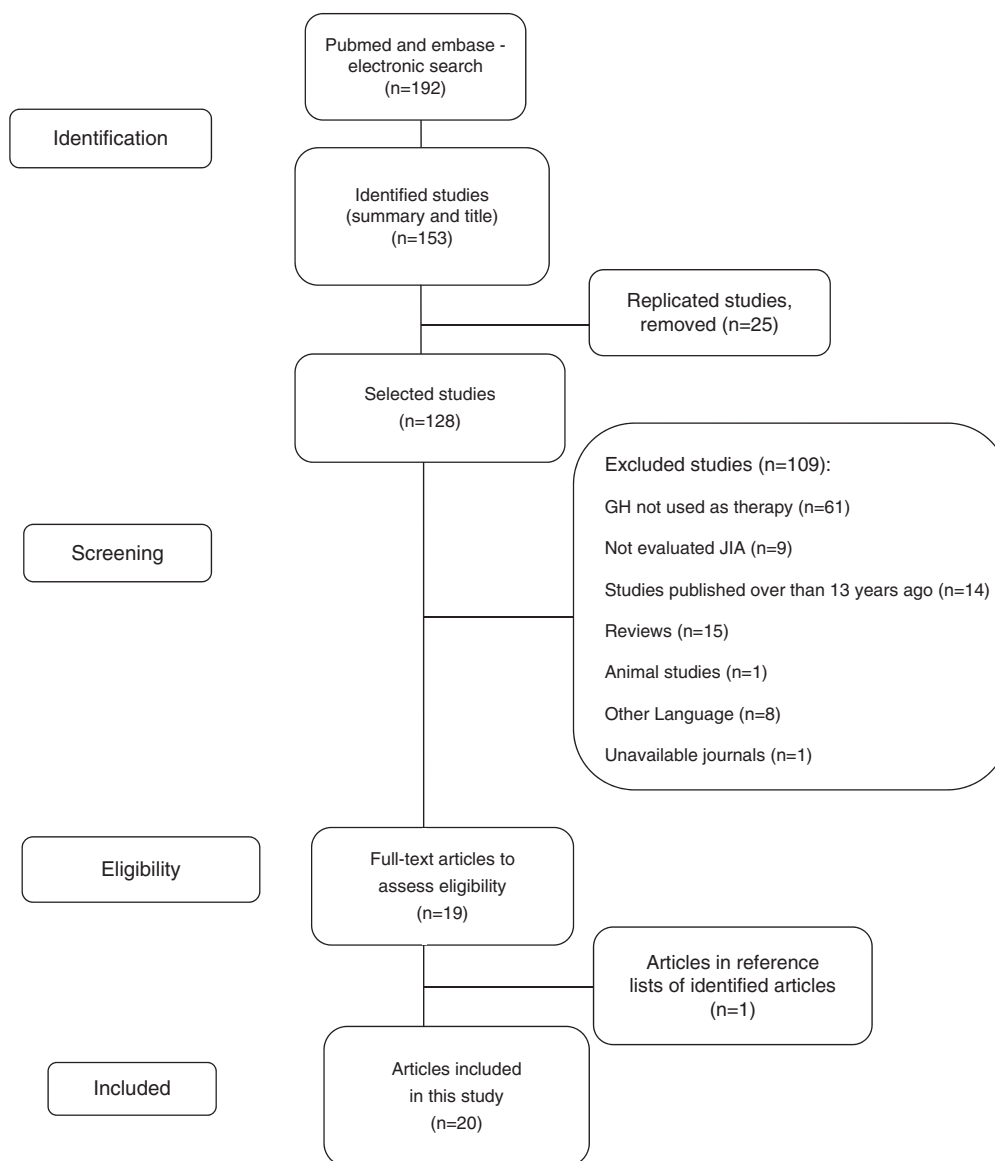


Fig. 1 – Explanatory diagram on the process of selection of articles.

evaluated patients with JIA; (5) Articles that included children and adolescents in their sample (Fig. 1).

Results

Twenty studies were included, of which 17 had longitudinal design^{5,11-25,28} and three were case reports.^{9,10,27} A total of 359 patients with JIA (systemic, polyarticular, and oligoarticular) were treated with GH, with doses ranging from 0.028 to 0.067 mg/kg/day, and aged from 4 to 17 years; the treatment time ranged from 9 months to 6 years (Tables 1 and 2).

After use of GH, an increased growth of JIA patients was demonstrated in 80% of the studies,^{5,11-25} and 35% reported significant improvement in pubertal development.^{11-13,16,17,24,25}

Among the positive effects of the treatment, 30% of the studies reported improvement in bone mineral

density and bone metabolism.^{12,17,19,21,23} In comparison with pre-treatment values, it was reported that the formation and resorption markers increased significantly during treatment,^{17,21,23} and that the plasma level of osteocalcin was the best variable predictive of growth in JIA patients who had been treated with GH.²¹

One study found that the fat level has remained stable, with no significant changes versus patients who did not use GH;¹² but in 4 (20%) studies, lean mass increase and fat mass decrease were observed.^{15,19,23,25}

Regarding blood glucose and glucose intolerance in 5 (25%) studies,^{14,19,24,25,28} a significant increase in fasting blood glucose was noted in patients treated with GH versus control group, which led, in some cases, to the possible development of insulin resistance,^{19,24,25,28} and to diabetes.^{25,28} Increases in glycosylated hemoglobin were also described.^{19,24,25}

Development of osteonecrosis¹⁰ was observed in one case report; in another report, one patient developed severe

Table 1 – Description of articles on Growth Hormone (GH) effects in patients with Juvenile Idiopathic Arthritis (JIA) (longitudinal studies): 1998–2015.

Article	Sample	Age group (years)	Disease duration (years)	GH dose (mg/kg/day)	Treatment duration (years)	GH effect
Bechtold, 2012 ¹¹ (Deutschland)	39 patients (systemic/polyarticular JIA) 24 controls	(8–13)	≅5	0.047	6.32 ± 1.96	GH had positive effects on height and pubertal development
Bismuth E, 2010 ²⁸ (France)	43 patients (systemic/polyarticular JIA) 15 controls	(4–14) (4–8)	3.9 ± 2.7 4.3 ± 2.9	0.065	3	GH combined with glucocorticoids was associated with a significant increase in fasting insulin level
Bechtold, 2010 ¹² (Deutschland)	12 patients (systemic/polyarticular JIA)	(9–14)	8.49 ± 2.9	–	5.35 ± 0.7	Benefits in anthropometric levels, and fat levels stabilized
Bechtold, 2007 ¹³ (Deutschland)	31 patients (systemic/polyarticular JIA) 18 controls	(10–14)	3,7 ± 1,2	0.047	8.4	Patients reached the height within the standard target set
Simon, 2007 ¹⁴ (France)	30 patients (systemic/polyarticular JIA)	(7–12)	–	0.065	3	Benefits in anthropometric levels Bone mineralization with no significant difference Increased blood glucose
Bechtold, 2005 ¹⁵ (Deutschland)	17 patients (systemic/polyarticular JIA)	(12–17)	8.2 ± 4.4	(0.036–0.047)	4	GH had positive and significant effects on height and muscle mass
Saha, 2004 ¹⁶ (Finland)	25 patients (12 polyarticular JIA, 10 oligoarticular JIA and 3 systemic JIA)	(8–11)	–	0.033	0.5 (6 months)	Patients with GH treatment grew faster versus control group
Bechtold, 2004 ¹⁷ (Deutschland)	11 patients (systemic/polyarticular JIA)	(9–11)	3.7 ± 1.4	0.047	4	Significant increase in height, and improvement in bone remodeling
Bechtold, 2003 ¹⁸ (Deutschland)	38 patients (systemic/polyarticular JIA)	(5.5–13.8)	≅3.8	(0.028–0.047)	4	Significant increase in final height
Simon, 2003 ¹⁹ (France)	30 patients (systemic/polyarticular JIA)	(6.8–13.0)	8.2 (4.5–15.6)	0.065	3	Improvement in growth rate Increases in lean body mass and bone mineral density Glucose intolerance observed in 6 patients Increase of glycosylated hemoglobin
Simon, 2001 ⁵ (France)	14 patients (systemic/polyarticular JIA)	≅9.7	≅3	0.065	1	Improved growth rate and prevention of metabolic complications
Al-Mutair, 2000 ²⁰ (Saudi Arabia)	10 patients (systemic/polyarticular JIA)	(6–15)	–	0.027	1 and 3	Improved growth in the final height One patient developed deformities in both knees
Touati, 2000 ²¹ (France)	14 patients (systemic/polyarticular JIA)	(6–14)	≅3	0.066	1	Significant increases in bone resorption markers Plasma level of osteocalcin was the best variable predictive of growth
Rooney, 2000 ²² (England)	20 patients (systemic/polyarticular JIA)	7.6	–	–	1	Improvement of bone metabolism and height
Simon, 2000 ²³ (France)	14 patients (systemic/polyarticular JIA)	≅9	–	0.06	2	Increases in growth rate and lean mass Increase in bone mineral density
Simon, 1999 ²⁴ (France)	14 patients (systemic/polyarticular JIA)	(9–12)	3 (9 months to ≅8 years)	0.067	1	Improvement in growth rate Decrease in glucose tolerance and increase in glycosylated hemoglobin levels
Touati, 1998 ²⁵ (France)	14 patients (systemic/polyarticular JIA)	≅9	–	0.066	1–2	Increase in growth Increase in lean mass and decrease in fat mass Increase of glucose tolerance and increase in glycosylated hemoglobin

Table 2 – Description of articles on Growth Hormone (GH) effects in patients with Juvenile Idiopathic Arthritis (JIA) (case reports): 1998–2015.

Article	Sample	Age group (years)	Disease duration (years ± SD)	GH dose (mg/kg/day)	Treatment duration (years)	GH effect
Kim, 2014 ⁹ (South Korea)	1 patient (Systemic JIA)	16	7	0.04	0.75 (9 months)	GH had positive effects on height Possible effect of GH on the reactivation of the disease
Nikishina, 2011 ¹⁰ (Russia)	1 patient (polyarticular JIA)	14	–	0.05	–	GH had positive effects on height Possible effect of GH in the development of osteonecrosis
Pun, 2011 ²⁷ (Canada)	1 patient (JIA + Autoimmune polyglandular syndrome type 1)	16	13	–	–	Atypical findings including growth hormone deficiency even with use of the treatment, short stature

deformity in both knees.²⁰ In case reports, reactivation of the disease in two studies^{9,10} and low final height in one study were observed.²⁷

Discussion

Recombinant GH has revolutionized the treatment of children and adolescents with growth hormone deficiency and other growth disorders, but the clinical and ethical controversies remain, about the diagnostic approach in patients with JIA, as well as the optimal dose, duration, and expected results.^{11,12,19,26}

The results obtained by many longitudinal studies confirmed previously published data, that the treatment with GH of patients with JIA allows positively affect the pubertal development and final height.^{5,11–25}

It is known that the treatment instituted, particularly the use of glucocorticoids, also compromise the growth, which depends on other factors such as age of onset of the disease, its severity, the patient's response to treatment, time of administration, and dose of the glucocorticoid administered.⁸

Bone formation and resorption markers increased significantly during the treatment with GH^{14,17,19,21–23}, but a study observed loss of growth following the discontinuation of the treatment.²³ It is believed that a prolonged treatment with GH is needed, in order to allow an assessment of a positive effect of this hormone on the bone density and metabolism in patients with JIA.^{10,14,17,19,23,25} The monitoring of patients to their final height, besides bone mass evaluation, are needed to better understand the potential beneficial effect of GH treatment.^{5,11–25,27}

As to glucose intolerance, studies did not find patients with abnormal glucose metabolism symptoms before use of GH.^{14,19,24,25,28} The metabolism of carbohydrates must be carefully monitored in JIA patients treated with GH, particularly during the acute phase of their disease. It is known that glucocorticoids interfere with the GH/IGF-1 axis, decreasing the GH pulsatile secretion by increasing of somatostatin levels and that these pharmaceuticals also reduce the expression of GH receptors on hepatocytes, causing some degree of resistance to GH, with a consequent reduction of IGF-1 levels.^{32,33}

Theoretically, GH not only regulates growth but also controls the immune function, considering that it is not common an occurrence of relapse of disease activity after several years of remission without a definite cause.^{18,25} It has been questioned if GH was responsible for the reactivation of the disease in those case reports presented in this paper.^{9,10}

One study reported an atypical case of JIA, with short stature after the use of GH; however, this result cannot be generalized to other studies because the patient suffered from other concomitant diseases.²⁷

It should be stressed that JIA is a disease with multiple clinical manifestations among affected individuals (a systemic, polyarticular, oligoarticular, etc., onset). Thus, there are no double-blind randomized controlled studies or trials with placebo versus the use of GH. A better understanding of the disease and more effective treatments in recent years can radically change the growth status of these patients. Some authors suggest that the treatment with GH is implemented in combination with other drugs, and biological drugs are among those most favored.³⁰

Conclusion

The studies published in recent years show improved growth and height rates in JIA patients treated with GH.

Some variation in the response to treatment was observed; in some cases, recovery in growth takes place, and in other cases the treatment prevents the loss of height generally observed during the natural course of the disease. The selection of the response depends on the initiation of treatment with GH and the on disease severity and activity. The studies presented in this review are singular, concerning the studied factors (positive and negative effects) and cannot be generalized. The combination of growth hormone with other drugs may be an option.

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Conflicts of interest

The authors declare no conflicts of interest.

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